REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

By the foregoing amendment, claims 11 and 21 have been amended. In particular, claim 11 has been amended so as to not be dependent upon canceled claim 6. Claim 11 is now dependent upon claim 8. Claim 21 has been amended to clarify applicants' invention. Support for the amendments to claim 21 can be found throughout the originally-filed application including, for instance page 21, lines 25-29, that talks of "pulmonary congestion that occurs as a result of cardiac dysfunction." No new matter has been added by the present amendments. Moreover, by the present amendments, applicants did not intend to limit the scope of any of the claims or element(s) recited therein.

Turning now to the Official Action, the Examiner has rejected claims 8-11 and 21 under 35 U.S.C. § 112, first paragraph as containing subject matter which allegedly was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. This rejection is respectfully traversed.

The invention of claim 21 is directed to a method for treating chronic heart failure by reducing pulmonary congestion, and is not, as alleged by the Examiner, directed to a method for treating chronic heart failure caused by reducing pulmonary congestion. Thus, the Examiner appears to have misunderstood the claim language. However, to expedite

prosecution in the present application and not to acquiesce to the Examiner's rejection, claim 21 has been amended consistent with the specification to recite a "method for treatment of cardiac dysfunction which produces pulmonary congestion . . . ."

In view of the above, it is evident that the claims did not, and now do not, introduce any new matter. Thus, withdrawal of this rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 8-11 and 21 have also been rejected under 35 U.S.C. §112, first paragraph, for purportedly failing to enable the full scope of the claims. This rejection is respectfully traversed.

To be enabling under §112, a patent application must contain a description that enables one skilled in the art to make and use the claimed invention. That some experimentation is necessary does not preclude enablement. The amount of experimentation simply must not be unduly extensive. *See, e.g., Atlas Powder Co. v. E. I. DuPont de Nemours & Co.*, 224 U.S.P.Q. 409, 413 (Fed. Cir. 1984).

First, the Examiner has argued that the present application does not reasonably provide enablement for "treatment of cardiac hypertrophy with ANP in species other than rats at dosages which do not cause diuretic and hypotensive effects[.]" See page 3 of the Official Action. Applicants respectfully disagree.

A rat hypercardia model is widely used for assessing the mechanism of hypercardia and the preventive and therapeutic efficacy of drugs. Although there are certainly differences in the expression subtypes of myosin heavy chain (MHC) between humans and

rats, hypertrophic stimulation by α-adrenergic, Ang. II, ET-1 and so forth is the same, and the compensatory increase in ANP expression during hypercardia also coincide between the two species. Although applicants used two types of animal models of the pressure loading type (aortic constriction) and volume loading type (arteriovenous shunt), these are models reflecting hypertensive and valvular hypercardia, respectively, in humans (Weinberg et al., *Circulation*, 1994, 90:1410-22; Liu et al., *Cir. Res.*, 1991, 69:52-58). Moreover, these models are also used for assessing ACE inhibitors and β-blockers currently used clinically for the treatment of heat failure, and simple vasodilators (hydralazine) have been reported to be ineffective (Bruckschelegel et al., *Hypertension*, 1995, 25:250; Linz et al., *Mol. Cell Biochem.*, 1995, 147:89; Ruzicka et al., *Circulation*, 1995, 91:16). Thus, the indication of hypercardia suppressive and recessive effects of ANP in these two types of rat models is considered by those skilled in the art to be representative of or provide reasonable support for efficacy in humans.

The present invention has novelty and an inventive step with respect to: (1) having indicated a suppressive effect on the formation of hypercardia at a dose level that does not affect blood pressure or urine volume in two types of models having different causes; and (2) having indicated effects that result in recession of hypercardia that has already formed, while also providing reasonable support for clinical effects.

In addition, the application to humans based on data obtained in animal models (such as with respect to pharmaceutical compositions and therapeutic methods) has been well recognized in U.S. patents (e.g., U.S. Patent No. 4,652,549). Moreover, the Federal

Circuit has indicated that *in vivo* testing in humans is not a requirement for satisfying the requirements of 35 U.S.C. §112, first paragraph. *See, e.g., In re Brana*, 34 USPQ2d 1437, 1442-43 (Fed. Cir. 1995).

Here, the PTO has not met its initial burden of providing evidence or scientific reasoning that the disclosed rat models are insufficient to support the claimed method for treating humans. Nonetheless, applicants have provided above sufficient evidence to establish the validity of the rat hypercardia model for human treatment as well.

Second, the Examiner has argued that the present application does not reasonably provide enablement for "treatment of cardiac hypertrophy with agents other than ANP and at dosages which do not cause diuretic and hypotensive effects." See page 3 of the Official Action. Applicants respectfully disagree with this allegation as well since compounds other than ANP act on CG-A sodium diuretic peptide receptors.

ANP and BNP are known to be specific ligands for CG-A sodium diuretic peptide receptors (GC-A receptors) that function as compounds which act on said receptors in humans (Koller et al., *Science*, 1992, 252:120). In addition, ANP and BNP are selective ligands of GC-A receptors in rats as well, and their affinity for GV-B receptors is known to be extremely low. Since there have been indicated to be no large species differences in their sensitivity, (Suga et al., *Endocrinology*, 1992, 130:229), one of skill in the art would recognize that it is sufficiently reasonable to apply information obtained in rats to humans. Moreover, the existence of receptors other than GC-A receptors that function as receptors

of ANP and BNP in any mammals, including humans and rats, have not been reported at the time of filing of the present application or at present.

Accordingly, the effects obtained in rats in the present application (effect on rats by which human ANP (hANP) was expressed) are considered to be sufficiently applicable to and provide reasonable support for humans, and are of an extent which could be easily carried out by a person with ordinary skill in the art without undue experimentation.

Moreover, in response to the Examiner's opinion that one of ordinary skill in the art would not know how to make or use the claimed invention with other compounds acting on GC-A receptors since the descriptions of the examples only pertain to ANP, applicants offer the following comments.

ANP was isolated and identified in 1984, while BNP was isolated and identified in 1989. Although their cDNA has been cloned, it has been suggested from their sequences that both are members of the same peptide family (Sudoh et al., *Biochem. Biophys. Res. Commun.*, 1989, 159:1427; Kambayashi et al., *FEBS Lett.*, 1990, 259:341). In addition, GC-A receptor was cloned as an ANP receptor in 1989 (Chinkers et al., *Nature*, 1989, 338:78), while GC-B was cloned as a similar receptor (Chang et al., 1989, 341:68; Schulz et al., *Cell*, 1989, 58:1155). As a result of studying the ligand selection of these receptors, it was known in 1991 that ANP and BNP both express physiological action mediated by GC-A receptors (Koller et al., *Science*, 1992, 252:120). At the time of filing of the present application and at present, there are no receptors other than GC-A receptors which have been clearly demonstrated to express the physiological action of ANP and BNP.

In addition, BNP was determined to demonstrate not only vasodilatory action and sodium diuretic action, but also aldosterone secretion inhibitory action (Higuchi et al., *Life Science*, 1989, 44:881) and acute cardiac insufficient therapeutic effects (Yamashita et al., *Circulation*, 1991, 84:1581) in the same manner as ANP by 1995, and it has also been determined that mouse expressing excessive BNP demonstrate the same phenotype as mice expressing excessive ANP (Steinhelper et al., *Hypertension*, 1990, 16:301; Ogawa et al., *J. Clin. Invest.*, 1994, 93:1911).

On the basis of the above, it was determined by 1996 that at least BNP expresses physiological action mediated by GC-A receptors in the same manner as ANP, and it would be reasonable for a person with ordinary skill in the art to expect that derivatives of ANP and BNP that act on GC-A receptors express hypercardia suppressive action at dose levels at which diuretic depressive action is not expressed in the same manner as ANP.

It can be seen from the above, that the present application reasonably provides enablement for the full scope of the claims. As such, the Examiner is respectfully requested to withdraw this rejection.

Lastly, the Examiner has rejected claims 8-11 and 21 under 35 U.S.C. § 103(a) as purportedly being obvious over Blaine or Berman in view of Cao et al. and Espiner. This rejection is respectfully traversed.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. The Examiner can satisfy this burden only by showing some objective teaching in the prior art

or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine or modify the relevant teachings of the references. *See, e.g., Ex parte Obukowicz*, 27 U.S.P.Q.2d 1063, 1065 (Bd. Pat. App. & Int. 1993). The Examiner cannot rely on applicants' own disclosure to reject a claim on prior art grounds. Rather, there must be a reason apparent at the time the invention was made to the person of ordinary skill in the art for applying the teachings at hand, or the use of the teaching as evidence of obviousness will entail prohibited hindsight. *See, e.g., Ex Parte Murphy v. Burford*, 217 U.S.P.Q. 479, 482 (PTO Bd. of App. 1982).

None of the cited references, taken alone or in combination as set forth by the Examiner above, teach or suggest the claimed invention. Rather, the Examiner has impermissibly used applicants' own disclosure in order to attempt to arrive at the claimed invention in hindsight.

Substances having diuretic depressive action are known through the examples of hydralazine and so forth to not necessarily have hypercardia inhibitory action and pulmonary congestion reducing action (Kojima et al., *Circulation*, 1994; 89:2204). Sodium diuretic peptides have been reported to inhibit DNA synthesis in cardiac fibroblasts cultured *in vitro*, and the paper of Cao et al. is cited in the specification of the present application as well.

However, whether or not sodium diuretic peptide, which was only known to have DNA synthesis inhibitory action in cultured cardiac fibroblasts *in vitro* and at the high concentration of 1 μM, not only demonstrates preventive effects on the formation of

hypercardia at a concentration of several 100 pg/mL, namely at a blood concentration of 1 nM or less, in two types of animal models having different causes in the form of pressure loading and volume location, but also be able to demonstrate effects to the extent of being able to recess hypercardia that has already formed, was not known nor could it have been reasonably predicted by one of ordinary skill in the art at the time of filing of the present application. Rather, this was demonstrated for the first time in the invention of the present application.

In addition, the efficacy of ANP in two types of corresponding animal models of hypertension (pressure loading) and valvular disorders (volume loading), which are considered to be causes of human hypercardia in consideration of its pathology in humans, and the ability to cause recession of hypercardia that has already occurred by a pressure loading hypercardia model (as a result of having therapeutic effects) were demonstrated for the first time in the present invention. Moreover, specification of the "dose levels at which diuretic depressive action is not expressed" was determined from the fact that both preventive and therapeutic effects in a hypertensive hypercardia model and preventive effects in a volume loading hypercardia model were achieved at the same dose level of ANP administration, the present invention is the first example of attaining suppression of pulmonary congestion and hypercardia without expressing diuretic or depressive action.

Since the invention of the present application is a method for treating chronic heart failure by reducing pulmonary congestion, it differs from the hypercardia therapeutic methods described in the references cited by the Examiner. In addition, the non-self-

evidence of a method for treating chronic heart failure based on the "action of reducing pulmonary congestion" in the advanced state of the disease of "chronic heart failure" is not negated in any way by a method for treating hypercardia, in which a state of heart failure has not been reached.

Without the use of impermissible hindsight reconstruction, one of ordinary skill in the art would not have been motivated to combine and/or modify the cited references in attempt to arrive at applicants' claimed invention. It is also emphasized, as discussed above in connection with the "new matter" rejection under 35 U.S.C. § 112, first paragraph, the claimed method is not directed to a method for treating chronic heart failure caused by reducing pulmonary congestion. Rather, the invention of claim 21 is directed to a method for treating chronic heart failure by reducing pulmonary congestion or, using the particular language of currently amended claim 21, is directed to a method of treating cardiac dysfunction which produces pulmonary congestions whereby the administered substance is in an amount effective for reducing pulmonary congestion and does not produce diuretic and hypotensive effects.

In view of the above, a proper *prima facie* case of obviousness has not been established. Therefore, withdrawal of this rejection is respectfully requested.

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions relating to this Amendment and Reply, or the application in general, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: February 19, 2004

By: _____
Susan M. Dadio
Registration No. 40,373

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

I hereby certify that this correspondence is being sent by Facsimile Transmission to Technology Center 1600, Commissioner For Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450 on:

Date: February 19, 2004
Name: Susan M. Dadio
(Typed or printed name of person signing the certificate)

Sign: _____
(Signature of person signing the certificate)

Date: February 19, 2004
(Date of Signature)